00005.001205.1 PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	Examiner: Sahar Javanmard
HIROSHI KASE, ET AL.	)	Group Art Unit: 1617
Application No.: 10/523,603	)	Confirmation No. 4143
Filed: February 4, 2005	)	
For: ADENOSINE A2A RECEPTOR ANTAGONISTS FOR TREATING RESTLESS LEGS SYNDROME OR NOCTURNAL MYOCLONUS (AS AMENDED)	)	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. §1.132

Sir:

I, Tomoyuki Kanda, Ph.D., do hereby declare as follows:

1. I attended Toyama Medical and Pharmaceutical University from 1985-1988 and received a Bachelors in Pharmacology in 1988.

2. From 1988-1990, I attended Graduate School of Pharmacology at Osaka University and received a Masters of Science in Pharmacology in 1990. I received my Ph.D. in Pharmacology in 1999.

3. I have been employed by Kyowa Hakko Kogyo Co., Ltd. (now Kyowa Hakko Kirin Co., Ltd.) since 1990. My positions there have been:

1990-2003	Researcher in Neuropharmacology
1993-1995	Visiting Research Fellow of the King's College London, University of London
2003-2008	Senior Researcher, Pharmacological Research Laboratories Pharmaceutical Research Center
2008-present	Senior Scientist, Pharmacological Research Laboratories Research Division

4. I have nearly 25 years experience in pharmacology, and more than 19 years experience conducting pharmacological research and development, including specializing in the field of treating Parkinson's disease, restless legs syndrome and Nocturnal Myoclonus.

5. I am familiar with the prosecution and claims of U.S. application No. 10/523,603, including the Examiner's rejection of claims 1-5 and 8-12 under 35 U.S.C. §103(a) as being obvious over U.S. Patent No. 5,587,378 in view of Trenkwalder, *Clin. Neurosci.*, Vol. 5 (1998) 107-14 and Evidente, *Movement Disorders*, Vol. 15, No. 2 (2000) 324-27.

6. I have prepared this Declaration in order to clarify the relationship among the etiology, pathology and clinical features of Parkinson's Disease, Restless Legs Syndrome and Nocturnal Myoclonus.

7. As is very well-understood by those of ordinary skill in this art, restless legs syndrome (RLS) is a sensorimotor disorder characterized by a distressed urge to move the legs and sometimes also other parts of the body, usually accompanied by a highly

marked sense of discomfort or pain in the legs or other affected body part. RLS is especially triggered by rest or inactivity, and its symptoms are temporarily relieved or suppressed by movement. Onset of RLS follows a circadian pattern, with symptoms most intense in the evening and nighttime hours, especially when the afflicted individual is lying down.

8. There are two types of RLS: idiopathic RLS, also known as "primary" RLS, which typically has a familial component, and "secondary" RLS, which typically occurs in conjunction with other medical conditions, particularly: iron deficiency anemia, pregnancy, and end-stage renal disease. The prevalence of RLS in large-scale population studies are from approximately 6% to 15% for the entire adult range[1]. The symptoms of RLS are frequently relieved by treatment with dopaminergic agents or opioids. Select anticonvulsants and sedative-hypnotics are also effective in some RLS patients.

9. Considerations of peripheral vs central nervous system pathology are based on pharmacologic studies. Dopaminergic agents that cross the blood-brain barrier alter RLS, with L-dopa and Dopamine agonists serving to reduce (and dopamine antagonists exacerbating) RLS symptoms[2]. However, dopamine antagonists with limited central action,[3] do not alter RLS symptoms. Thus, combination of a peripheral dopamine

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1 Lavigne et al., "Restless legs syndrome and sleep bruxism: prevalence and association among Canadians", *Sleep*, Vol. 17, No. 8 (1994) 739-43.

2 de Mello, et al., "Treatment of periodic leg movements with a dopaminergic agonist in subjects with total spinal cord lesions", *Spinal Cord*, Vol. 87, No. 9 (1999) 694-7, Yokota T, Hirose K, Tanabe H, Tsukagoshi H, "Sleep related periodic leg movements (noctural myoclonus) due to spinal card lesion", *J. Neurol. Sci.*, Vol. 104, No. 1 (1991) 13-8.

3 Such as domperidone.

antagonist together with a central dopamine agonist has been used to successfully reduce adverse effects without altering the efficacy of the treatment[4].

10. These do not teach or suggest a link or any causality between RLS and Parkinson's disease. Specifically, (i) Parkinson's disease does not at all increase the risk for RLS and (ii) RLS does not at all increase the risk for Parkinson's disease.[5] For example, the prevalence of RLS in Parkinson's disease patients is approximately 10-15%, which is not significantly different than the prevalence of RLS in the general population, and which is also not significantly different than the prevalence of RLS in other conditions[6], i.e. 11.9 to 19.4% of pregnant women suffer from RLS, and 6 to 83% patients with end stage renal disease suffer from RLS.[7]

11. These results all indicate that RLS and Parkinson's disease do not share the same pathophysiologic mechanism.[8]

12. Both RLS and Parkinson's disease have dopaminergic dysfunction in the central nervous system - - A9 dopaminergic neurons are involved in Parkinson's disease, and A11 dopaminergic neurons may be involved in RLS. As discussed above, central acting dopaminergic antiParkinsonian agents are effective in treating RLS since

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[4] Wetter et al., "A randomized controlled study of pergolide in patients with restless legs syndrome", *Neurology*, Vol. 52, No. 5 (1999) 944-50.

[5] To the contrary, the common connection between RLS and Parkinson's disease appears to be only the iron deficiencies that can play a role in both conditions.

[6] Tan et al., "Restless legs syndrome in Parkinson's disease", *J. Neurol. Sci.*, Vol. 196 (2002) 33-6.

[7] Goodman et al., "Restless leg syndrome in pregnancy", *Brit. Med. J.*, Vol. 297, No. 6656 (1988) 1101-2; Collado-Seidel et al., "Clinical and biochemical findings in uremic patients with and without restless legs syndrome", *Am. J. Kidney Dis.*, Vol. 31, No. 2 (1998) 324-8.

[8] To the contrary, antiParkinsonian agents such as anticholinergics are <u>not</u> effective in treating RLS.

they correct the central nervous system. That is, such agents all have dopaminergic action in the CNS, i.e., L-DOPA is a dopamine precursor; pramipexol, ropinirole and rotigotine are dopamine receptor agonists; and amantadine increases dopamine synthesis and release, or inhibits dopamine reuptake. Thus, these agents treat RLS as only central acting dopaminergic agents, and not as antiParkinsonian agents.

13. Therefore, a person of ordinary skill in this art, who understands the foregoing RLS physiopathology, also understands that there is no reason to arbitrarily administer antiParkinson disease medication to RLS patients unless such medication is also a central acting dopinamergic agent. In contrast to this, however, the compounds of the pending claims are not central acting dopinamergic agents. Instead the compounds of the pending claims are adenosine A2A receptor antagonists.

14. As to noctural myoclonus, such is a disorder characterized by aching or burning sensations in the lower (and rarely, the upper) extremities that occur prior to sleep, or may awaken the patient from sleep. The patient irresistibly moves the affected limbs to bring temporary relief, thus disrupting sleep and so, resulting in daytime hypersomnolence.[9] RLS differs essentially from noctural myoclonus in that in noctural myoclonus (i) the individual reports no adverse sensory stimuli and (ii) it is primarily a sleep-associated movement disorder[10], neither of which is true for RLS.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further these statements were made with the knowledge that willful false statements and

[9] Harrison's Principles of Internal Medicine, 15th ed., 159.

[10] Adams, et al., *Principles of Neurology*, 6th ed., 387; *Schmerz Rundsch Med. Prax.*, Vol. 86, No. 18 (1997) 732-36.

the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Tomoyuki Kanda, Ph.D.

Date: 17th Jul. 2009

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